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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TRAN, MY CHAU T	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 08/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,426	MORTENSEN ET AL.	
	Examiner	Art Unit	
	My-Chau T. Tran	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28,30-32 and 34-48* is/are pending in the application.

4a) Of the above claim(s) *1-25 and 38-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-28,30-32,34-37 and 45-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *22* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment filed 4/21/03 in Paper No. 20 is acknowledged and entered. Claims 26-27 and 47 are amended by the amendment. Claim 48 is added by the amendment.

2. Claims 1-28, 30-32, 34-48 are pending.

Election/Restrictions

3. Claims 1-25 and 38-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

4. This application contains claims 1-25 and 38-44 are drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

5. Claims 26-28, 30-32, 34-37 and 45-48 are treated on the merit in this Office Action.

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections

7. Claims 26-28, 30-32, and 45-48 (*new claim 48 is included*) are rejected under 35 U.S.C. 103(a) as being unpatentable over Chick et al. (US Patent 6,040,194) in view of Bernard et al. (*Analytical Biochem*, 255:101-107, 1998).

Chick et al. disclose using FRET (fluorescence resonance energy transfer) for analytes detection (col. 3, lines 9-24). The reagent (composition) includes two components, one of which is labeled with an energy-absorbing donor molecule and the other is labeled with an energy-absorbing acceptor molecule. The fluorescence associated with the resonance energy transfer from donor and acceptor (FRET) is measured (col. 3, lines 15-19). The components could be members of a specific binding pair or ligands that bind specifically to different portions of the analyte (col. 3, lines 19-24). The donor and acceptor pair can be fluorophores (col. 7, lines 37-67 to col. 8, lines 1-3). The fluorophore can be covalently attached to the components ((col. 10, lines 19-41). The analytes include enzymes, antibodies, antigens, polynucleotides (col. 5, lines 15-32 and 52-56) or combination of antibody-antigen, receptor-ligand, and enzyme-substrate (col. 9, lines 43-50) (referring to claim 30-32 and 46). In the embodiment where two ligands that binds to different portions (sites) of the analyte molecule, the ligands could be antibodies and are labeled with the fluorophores (col. 10, lines 18-35) (referring to an indirect attachment).

Further with regard to the new claim 48, the limitation (e.g. *"wherein said indirect attachment is effected through a linking moiety selected from the group consisting of an antibody, antibody fragment, biotin and streptavidin"*) was previously presented in the amended claim 26 (e.g. twice amended). The limitation was address with regard to the "indirect attachment" (see last sentence of the above paragraph).

Chick et al. do not expressly disclose that the donor-acceptor pair is fluorescein and cyanine 5.

Bernard et al. discloses binding pair, which is a complementary oligonucleotide (pg. 101, right col. 2nd paragraph; pg. 102, left col., lines 1-2 and 4-8). A member of the binding pair is directly attached to fluorescein (a complementary fluorescein probe) and the other member of the binding pair is directly attached to cyanine 5 (a Cy5-labeled PCR strand) (pg. 102, left col., lines 4-8). The binding pair is associated so that the fluorescein and cyanine 5 are in fluorescence resonance energy transfer to each other (pg. 102, left col., lines 30-44).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include fluorescein and cyanine as the donor-acceptor pair in FRET as taught by Bernard et al. for the donor-acceptor pair in the composition of analytes detection using FRET of Chick et al. One of ordinary skill in the art would have been motivated to include fluorescein and cyanine as the donor-acceptor pair in FRET in the composition of analytes detection using FRET of Chick et al. because Chick et al. disclose that any combination of donor-acceptor pair can be use in FRET (col. 7, lines 37-41). Bernard et al. teaches that the combination of fluorescein and cyanine can be use as a donor-acceptor pair in FRET (pg. 102, left col., lines 30-44). Therefore, the choice of donor-acceptor pair for FRET would depend on the availability of fluorophores.

Response to Arguments

8. Applicant's argument(s) directed to the above rejection under 35 USC 103(a) as being unpatentable over Chick et al. (US Patent 6,040,194) in view of Bernard et al. (*Analytical*

Biochem, 255:101-107, 1998) for claims 26-28, 30-32, and 45-47 were considered but they are not persuasive for the following reasons.

Applicant alleges that "[N]either Chick nor Bernard, alone or combined, discloses an indirect linkage of the fluorophores to the reagent components as claimed presently. Given the requirement in Chick that the excited state energy level of the donor must overlap with the excited state energy level of the acceptor (see column 6, lines 19-21) and given the teaching in Bernard that the fluorescence of the fluorescein is set forth as being within the range of 520-560 nm, and that of Cy5 as being within the range of 655-695 nm, Applicants contend that these two references are not capable of being combined to arrive at the claimed invention."

Applicant's arguments are not convincing since Chick et al. do disclose "an indirect linkage of the fluorophores to the reagent components as claimed presently." Chick et al. disclose "[T]he second approach using FRET is to select two ligands that bind to different portions (sites) of the analyte molecule; in addition to being spatially different, the portions may be chemically different as well" (col. 10, lines 18-21). That is the first ligand is directly bonded to one of the pair of fluorophores and bind to the analyte (e.g. binding pair). The second ligand binds to a different site of the analyte and is bonded to the second pair of fluorophores (e.g. acts as the indirect linkage between the second pair of fluorophores with the analyte). Chick et al. further disclose that "[T]he ligands could be two antibodies, two cell receptors, or an antibody and a cell receptor" (col. 10, lines 25-26) (refers to new claim 48). Thus Chick et al. do disclose "an indirect linkage of the fluorophores to the reagent components as claimed presently" with regard to new claim 48.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Bernard et al. teach that "fluorescence resonance energy transfer occurs between adjacent fluorescein-labeled and Cy5-labeled hybridization probe" (pg. 101, line 34 to pg. 102, lines 1-2). Both Chick et al. and Bernard et al. teach the method of detecting binding of "receptor-ligand" binding pair by fluorescence resonance energy transfer (e.g. analogous art) therefore there is reasonable expectation of success to fluorescein and cyanine 5 as the donor-acceptor pair in fluorescence resonance energy transfer. Therefore, Chick et al. in combination with Bernard et al. is obvious over the presently claimed invention.

9. Claims 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chick et al. (US Patent 6,040,194) in view of Bernard et al (*Analytical Biochem*, 255:101-107, 1998) as applied to claims 26-28, 30-32, and 45-48 above, and further in view of Dykens et al. (US Patent 6,280,981 B1).

The composition using FRET (fluorescence resonance energy transfer) for analytes detection of Bernard and Chick applied for the reasons discussed above.

Both Bernard and Chick do not expressly disclose the proximity of the fluorescence resonance energy transfer.

Dykens teaches that the efficiency of the resonance energy transfer is dictated largely by the proximity of the donor and acceptor (col. 15, line 38-52) and that those familiar with the art will readily appreciate that donor-acceptor intermolecular distance is a cardinal determinative factor for the efficiency of the resonance energy transfer (col. 31, line 14-17). Dykens et al list the proximity distance in col. 31, line 1-9.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to include the proximity of the fluorescence resonance energy transfer as taught by Dykens in the composition of analytes detection using FRET of Chick et al. as modify by Bernard et al. One of ordinary skill in the art would have been motivated to include the proximity of the fluorescence resonance energy transfer in the composition of analytes detection using FRET of Chick et al. as modify by Bernard et al. for the advantage of providing a more efficient determination the resonance energy transfer in different combination of binding pair. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233.

Response to Arguments

10. Applicant's argument(s) directed to the above rejection under 35 USC 103(a) as being unpatentable over Chick et al. (US Patent 6,040,194), Bernard et al. (*Analytical Biochem*, 255:101-107, 1998), and Dykens et al. (US Patent 6,280,981 B1) for claims 34-37were considered but they are not persuasive for the following reasons.

Applicant contends that "[N]either Chick nor Bernard, alone or combined, discloses an indirect linkage of the fluorophores to the reagent components as claimed presently. Given the

requirement in Chick that the excited state energy level of the donor must overlap with the excited state energy level of the acceptor (see column 6, lines 19-21) and given the teaching in Bernard that the fluorescence of the fluorescein is set forth as being within the range of 520-560 nm, and that of Cy5 as being within the range of 655-695 nm, Applicants contend that these two references are not capable of being combined to arrive at the claimed invention." Therefore, Chick et al. Bernard et al., and Dykens et al. are not obvious over claims 34-37.

Applicant's arguments are not convincing since Chick et al. in combination with Bernard et al. is obvious over the presently claimed invention as discuss above (e.g. in response to the rejection under 35 USC 103(a) as being unpatentable over Chick et al. (US Patent 6,040,194) in view of Bernard et al (*Analytical Biochem*, 255:101-107, 1998) for claims 26-28, 30-32, and 45-47). Therefore Chick et al. Bernard et al., and Dykens et al. are obvious over claims 34-37.

New Rejections – Necessitated by Amendment

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 26-27, 34-37, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ju (US Patent 5,814,454) and Wittwer et al. (US Patent 6,140,054).

Ju disclose a composition comprising "[S]ets of fluorescent labels, particularly labeled primers" (e.g. binding pair is complementary oligonucleotides) wherein "[A]t least two of the labels of the subject sets comprise a common donor and acceptor fluorescer component in energy transfer relationship separated by different distances, such that the labels provide distinguishable fluorescent signals upon excitation at a common light wavelength" (e.g. fluorescence resonance energy transfer) (col. 2, lines 31-47). Both the donor and acceptor fluorescer components are covalently bonded to the primer (e.g. direct attachment) (col. 3, lines 35-36) or through a linker group (e.g. indirect attachment) (col. 6, lines 56-62). The fluorescence resonance energy transfer proximity range is from about 4 to 200 Å (col. 5, lines 42-53) (refers to claims 34-37).

The composition of Ju does not expressly disclose that the donor and acceptor fluorescer component are fluorescein and cyanine 5 (e.g. Cy5).

Wittwer et al. disclose a composition comprising "[F]RET oligonucleotide pair comprises a pair of oligonucleotide probes including a donor oligonucleotide probe, labeled with a resonance energy transfer donor, and an acceptor oligonucleotide probe, labeled with a resonance energy transfer acceptor" (col. 4, lines 30-36). The donor and acceptor fluorescer components are fluorescein/Cy5 or fluorescein/Cy5.5 (col. 9, lines 7-21).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include fluorescein and cyanine 5 (e.g. Cy5) as the donor and acceptor fluorescer component as taught by Wittwer et al. in the composition of Ju. One of ordinary skill in the art would have been motivated to include fluorescein and cyanine 5 (e.g. Cy5) as the donor and acceptor fluorescer component in the composition of Ju for the advantage of providing an excellent resonance energy transfer pair for hybridization monitoring (Wittwer: col. 8, lines 56-60) since both Ju and Wittwer et al. disclose the method of detecting DNA hybridization using fluorescence resonance energy transfer (Ju: col. 12, lines 16-25; Wittwer: col. col. 8, lines 56-60).

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to My-Chau T. Tran whose telephone number is 703-305-6999. The examiner is on Increased Flex Schedule and can normally be reached on Monday: 8:00-2:30; Tuesday-Thursday: 7:30-5:00; Friday: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang can be reached on 703-306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

mct
August 14, 2003

PADMASHRI PONNALURI
PRIMARY EXAMINER